Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Dec. 49 p. (Technology appraisal guidance; no. 327).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Dabigatran etexilate is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Cardiology

Geriatrics

Hematology

Internal Medicine

Preventive Medicine

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis (DVT) and/or pulmonary embolism (PE)

Target Population

Adult patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE)

Interventions and Practices Considered

Dabigatran etexilate

Major Outcomes Considered

- Clinical effectiveness
  - Mortality
  - Venous thromboembolism recurrence
  - Complications following deep vein thrombosis (DVT) or pulmonary embolism (PE) including post-thrombotic syndrome, heart failure, and chronic pulmonary hypertension
  - Adverse events of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding)
  - Health-related quality of life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the BMJ Technology Assessment Group (BMJ-TAG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description and Critique of Manufacturer's Search Strategy

The manufacturer reports that the systematic review searches were performed in two phases. Phase 1 was to identify studies investigating dabigatran, rivaroxaban, edoxaban, and apixaban. Phase 2 was comprised of searches for unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and fondaparinux.

In the manufacturer's submission (MS) it is reported that the following databases were searched during phase 1 and 2:

- MEDLINE and MEDLINE In-Process (using PubMed platform)
- EMBASE (using Dialog Platform)
- The Cochrane Library, including the following:
    - The Cochrane Database of Systematic Reviews
    - The Cochrane Central Register of Controlled Trials
    - Database of Abstracts of Reviews of Effectiveness
- Biosciences Information Service (using the Dialog Platform)

The manufacturer reported that the phase 1 searches of electronic databases (for studies of dabigatran, rivaroxaban, edoxaban, and apixaban) were performed on 23 July 2012 and the phase 2 searches (for UFH, LMWH, and fondaparinux studies) were performed on 1 October 2012.

The manufacturer used a combination of free-text search terms and Medical Subject Heading (MESH) terms covering the following:

- Population of interest: treatment and secondary prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Interventions of interest: dabigatran, rivaroxaban, edoxaban, apixaban, warfarin, UFH, LMWH (including enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin), and fondaparinux
- Study types: randomised controlled trials (RCTs) and non-randomised studies
- Exclusions: comments, editorials, letters, case reports, or studies in animals but not humans

The ERG notes that, according to the search strategies provided, search terms for phase 1 clinical trials were also used in the search strategies to exclude phase 1 trials from both the phase 1 and phase 2 searches. In addition, as highlighted by the manufacturer, the ERG notes that the phase 2 database searches included terms restricting the phase 2 search results to including only RCTs, i.e., observational data were excluded. The ERG considers this to be appropriate as any observational data identified through the phase 2 searches would not have been expected to provide any head-to-head data on the safety or efficacy of dabigatran. The ERG considers that observational data on dabigatran would have been identified in the phase 1 searches.

The manufacturer also conducted searches of internet websites and selected conference abstracts. The websites and conference abstracts that were searched included:

- International Society on Thrombosis and Haemostasis

- Hematology Association
- ClinicalTrials.gov Web site (searched for ongoing trials);
- National Institute for Health and Care Excellence (http://www.nice.org.uk/)
- Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/index.php/en/home)
- German Institute for Quality and Efficiency in Healthcare
- Pharmaceutical Benefits Advisory Committee, Australia (http://www.health.gov.au/internet/main/publishing.nsf/Content/health-publicat.htm)
- Scottish Medicines Consortium (http://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory)

The phase 1 internet searches were carried out on 19 and 20 July 2012, and the phase 2 internet searches between 11 and 13 October 2012. The ERG notes that the searching of conference abstracts was limited to abstracts that were published between January 2010 and July 2012. There is a minor discrepancy in the MS text and the appendices regarding the end date for the phase 1 conference abstract searches: 23 July vs 19 July. The phase 2 searches were conducted on 13 October.

All of the searches were updated in 2014 with the electronic database searches being conducted on 28th April 2014 with date limitations of 9 July 2012 to present phase 1 and 16 September 2012 to present phase 2. The internet searches were updated between 28th April and 1st May 2014 and limited to data published after 9 July 2012.

There was no restriction based on language applied in the database search strategies used by the manufacturer. In addition, the manufacturer reports that foreign-language sources that appeared relevant at the screening stage were extracted by linguists to determine their eligibility for inclusion.

The ERG considers the manufacturer to have conducted comprehensive searches using a variety of different sources including electronic medical databases and internet website pages. In addition, the manufacturer reports reviewing bibliographic reference lists of included studies, reviews, meta-analyses, and health technology assessment (HTA) documents. The ERG also considers the manufacturers search terms and restrictions to be appropriate for the systematic review.

Inclusion/Exclusion Criteria Used in Study Selection

The manufacturer reports that the study selection process occurred in the following two phases:

- Level 1 screening: Titles and abstracts of studies identified from the electronic databases and from Internet searches were reviewed for eligibility by one researcher. A second researcher independently screened a random sample of 5% of the records. Any differences were resolved by consensus.
- Level 2 screening: Full texts of studies selected at level 1 were obtained and reviewed for eligibility by one researcher, using the same inclusion and exclusion criteria as used in level 1 screening. A second researcher independently screened a random sample of 5% of the records with any differences resolved by consensus.

In addition, the manufacturer reports that the second researcher reviewed all studies selected after the level 2 screening to confirm their eligibility. The MS suggests that foreign-language sources were excluded at the level 2 screening stage. The ERG are unsure as to why there were no language restrictions in the database searches and why linguists were involved in assessing foreign language publications during level 1 screening if they were subsequently excluded based on language of publication at level 2 screening. In addition, the ERG is unsure as to the impact excluding foreign language publications may have had.

Table. Inclusion and Exclusion Criteria for Systematic Review

Criteria	Included	Excluded
Study Type	• Randomised, controlled prospective clinical trials • Non-randomised, controlled prospective clinical trials • Long-term follow-up studies (e.g., open-label follow-up studies)	• Prospective observational studies (e.g., phase 4 studies) • Preclinical studies • Phase 1 studies • Prognostic studies • Retrospective studies

Criteria	Included	Excluded
		• Case reports • Commentaries and letters (publication type) • Consensus reports • Reviews, systematic reviews, and meta-analyses (however, reference lists were reviewed for any relevant studies)
Patient Populations	Patients with DVT and/or PE receiving treatment or secondary prevention for recurrent DVT and/or PE	Patients receiving primary prophylaxis for prevention of a first DVT or PE event
Interventions	• Dabigatran, rivaroxaban, edoxaban, and apixaban • Warfarin (secondary prevention trials only) • UFH or LMWH (all agents, including, but not limited to, enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin) given for more than 10 days, i.e., long-term or extended treatment only (trials investigating acute parenteral treatment with heparin, e.g., for 5-10 days followed by a vitamin K antagonist, were not included as heparin trials) • Fondaparinux (given for 7 or more days)	Studies that do not include any of the interventions in the inclusion criteria list
Outcomes	• Recurrent DVT or PE • Bleeding • Death	

The ERG note that the study inclusion criteria included non-randomised, controlled prospective clinical trials and long-term follow-up studies (e.g., open-label follow-up studies) but one of the exclusion criteria is prospective observational studies (e.g., as phase 4 studies). The ERG is unsure as to which observational studies would be excluded or the definition of long-term used. The ERG notes that no observational studies were included in the manufacturer's review of clinical effectiveness and so the ERG is unable to comment further on this.

The ERG also notes that the manufacturer included edoxaban and apixaban as potential comparators of interest although they were not requested in the final scope issued by NICE. The manufacturer does not present data for these two drugs within the MS although the ERG notes that apixaban has been included in a network meta-analyses (NMA) in the supplementary meta-analysis report supplied by the manufacturer.

Refer to Section 4 in the ERG report for more information on the literature search.

Cost-effectiveness

ERG Comment on Manufacturer's Review of Cost-effectiveness Evidence

The manufacturer carried out a systematic review of the economic literature to identify cost-effectiveness publications relevant to the use of dabigatran for the acute treatment and secondary prevention of DVT and PE. Details of the search strategy, inclusion and exclusion criteria, data extraction tables, and study quality assessment were provided within the submission.

The following electronic databases were searched: MEDLINE; MEDLINE In-Process; EMBASE; EconLit; BIOSIS; the Cochrane Library. The search was carried out in February 2013 and updated in April 2014. Search terms captured the condition of interest (DVT/PE), a range of interventions, and economic evaluation studies. Publications dated from the year 2000 were included in the review; the restriction on date was justified by the manufacturer "because economic data published before that time were unlikely to be relevant to current treatment practices, resource patterns, and costs."

In addition to database searches, a number of internet searches were carried out to identify conference abstracts and published health technology

assessments (HTAs). The internet searches were carried out in February 2013, and updated during April and May 2014. Conference abstracts were limited to those published from January 2011; the restriction on date was justified by the manufacturer "as high-quality studies reported in abstract form before 2011 were expected to have been published in a peer-reviewed journal." No date restriction was applied for HTA documentation. Reference lists of included cost-effectiveness studies were also reviewed.

The inclusion and exclusion criteria applied are considered to be reasonable, with the exception of the choice of included interventions. The manufacturer elected to restrict included studies to those which evaluated at least one of the following treatments: apixaban, dabigatran, edoxaban and rivaroxaban. Economic analyses and cost studies comparing LMWH, UFH, warfarin and fondaparinux, that did not evaluate apixaban, dabigatran, edoxaban or rivaroxaban were identified but not formally included in the review.

Refer to Section 5 in the ERG report for more information on the ERG critique of the manufacturer's search strategy for cost-effectiveness evidence.

Number of Source Documents

Clinical Effectiveness

- After deduplication, the manufacturer's searches resulted in 4,425 articles from the phase 1 searches, 4,944 from phase 2, and a total of 1,155 from the update searches of phase 1 and phase 2. Following abstract and full text screening, a total of 42 studies from 41 publications were included. Six of the studies were identified through the update search.
- The manufacturer reported that 29 of the studies investigated acute treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and 13 of the studies investigated secondary prevention. In terms of the 29 acute treatment studies, the manufacturer reported that four studies investigated dabigatran, three studies investigated rivaroxaban, 19 studies investigated low molecular weight heparin (LMWH), of which two also included unfractionated heparin (UFH), two studies investigated apixaban and one study investigated edoxaban.

Cost-effectiveness

- A total of 12 cost-effectiveness analyses were identified from the original search (5 studies) and the updated search (7 studies). Of the 12 studies, three were carried out from the perspective of the UK. One of these studies related to a manufacturer submission for NICE TA261; a single technology assessment (STA) appraising the use of rivaroxaban for the treatment of acute DVT and secondary prevention of DVT and PE. The remaining two UK studies were conference abstracts; the manufacturer reported that both studies were published in 2013. The manufacturer did not provide the full references for these studies and the Evidence Review Group (ERG) was unable to identify these papers.
- The manufacturer submitted a *de novo* Markov cost-utility model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an

independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the BMJ Technology Assessment Group (BMJ-TAG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Data Extraction

The manufacturer reported that the following data fields were included in the data extraction:

- Trial acronym (if available)
- First author and year of the primary report
- Identity of any linked secondary reports
- Interventions (including dosages, duration of treatment, and type and duration of previous anticoagulation treatment) and associated patient numbers
- Patient population (key disease information, such as whether patients had deep vein thrombosis (DVT) and/or pulmonary embolism (PE); cause of DVT and/or PE; risk factors; time from onset of qualifying events or symptoms; previous DVT and/or PE; comorbidities; and key demographic information, such as age and percentage of the cohort that was female or male, and creatinine clearance)
- Whether the trial was blinded (single blind, double blind)
- Identification of the primary and key secondary outcome measures that were defined
- Duration of follow-up
- Results for the clinical outcomes of interest (if available)

In addition, the manufacturer reported that data were extracted from full-text versions of studies or clinical study reports, where available. The manufacturer also reported that quality-control procedures for the data extraction included verification of all extracted data with their original sources by a second researcher. The ERG considers this to be an acceptable method of data extraction.

Quality Assessment

The manufacturer conducted a quality assessment for the trials included in the systematic review using what appears to be the Cochrane risk of bias tool. A summary of the manufacturer's quality assessment for the four key trials presented within the manufacturer's submission (MS) are presented in Table 4 in the ERG report.

In general the ERG agrees with the manufacturer's quality assessment for each of the four trials. However, the ERG considers it important to highlight the manufacturer's response to "Did the analysis include an intention-to-treat analysis?". The studies utilised a modified intention-to-treat (mITT) approach with only patients receiving at least one dose of study medication being included in the analyses (referred to by the manufacturer as the final analysis set [FAS]). Supplementary intention-to-treat (ITT) data were provided to the ERG for the primary outcome at the clarification response stage. The ERG notes that the number of patients in the FAS was slightly lower than the number in the ITT population. However, as the difference in numbers between the ITT and FAS is small, the ERG does not consider it likely to have much impact on the overall results.

Description and Critique of the Indirect Comparisons and Network Meta-Analyses

The manufacturer conducted both adjusted indirect comparisons (AICs) and network meta-analyses (NMAs) to provide relative treatment effect estimates between dabigatran and rivaroxaban for efficacy and safety endpoints. The inclusion/exclusion criteria for the AIC and NMA are detailed in Table 66 in the ERG report.

The methods used for abstract appraisal, study inclusion, data extraction and quality assessment were the same as those reported above.

There were no head-to-head trials identified comparing dabigatran to rivaroxaban and so the manufacturer conducted an indirect comparison using the available trial data. There are several different methods commonly used to compare treatments that have not been investigated in head-to-head trials. The manufacturer chose to use two different approaches, AIC and NMA (also known as mixed treatment comparison [MTC]). The manufacturer reported only the results of the AIC in the MS. However they also provided the data and results used in the NMA in a separate report. The manufacturer's rationale for presenting the AIC results was: ".... a mixed-treatment comparison of all trials was performed. However, the results of this approach were not used further since the evidence network did not include mixed evidence from head-to-head trials and indirect evidence and hence did not add additional information." The ERG does not consider this to be a justification for using AIC over NMA as there were more than 2 interventions of interest in each NMA and so using an AIC methodology limits the ability to compare outcomes between the different treatments. This is because the resulting point estimates from multiple AICs, despite using the same baseline treatment, are not directly comparable. In contrast, the resulting point estimates for different treatments from an NMA are comparable. The ERG thus considers the results of the manufacturers NMA to be of potential importance.

Refer to Section 4 in the ERG report for additional information on the analysis of clinical effectiveness studies.

Cost-effectiveness

Model Structure Developed by the Manufacturer

The manufacturer developed a *de novo* Markov cost-utility model in Microsoft Excel®. The model followed an average cohort through a lifetime time horizon in the base case, with a cycle length of one month (assumed to be 30 days). The manufacturer analysed two separate scenarios:

- Acute treatment of DVT and PE only (hereafter referred to as "acute treatment")
- Acute treatment of DVT and PE followed by secondary prevention of future DVT and PE (hereafter referred to as "treatment and secondary prevention")

The acute treatment scenarios specifically related to a model in which people only receive acute treatment for their initial or recurrent DVT/PE. The treatment and secondary prevention scenarios specifically related to a model in which people receive acute treatment and secondary prevention for their initial DVT/PE, and acute treatment only for their recurrent DVT/PE. This is described in greater detail in Section 5 in the ERG report.

The model structure is presented in Figure 11 in the ERG report. The model structure applied to both the acute treatment, and the treatment and secondary prevention scenarios.

All patients begin in the "Index Venous Thromboembolism (VTE)" health state as having confirmed symptomatic (proximal) DVT, or confirmed symptomatic PE (with or without proximal DVT). These patients receive acute treatment with dabigatran (with 5 days parenteral low-molecular-weight heparin [LMWH] treatment), warfarin (with 5 days parenteral LMWH treatment), rivaroxaban, or LMWH (for people with active cancer). Patients who also receive secondary prevention at treatment for their initial VTE event (i.e., those in the treatment and secondary prevention scenario) additionally receive 6 to 18 months of treatment with dabigatran (duration depends upon the comparator selected), warfarin (18 months), rivaroxaban (6 months) or LMWH (6 months).

If a patient completes treatment (either acute treatment or secondary prevention) or withdraws from treatment (due to recurrent VTE, a major bleeding event [MBE], an adverse event, worsening of other pre-existing conditions, non-compliance with protocol, loss to follow-up, removal of consent), they transition to the "off treatment" health state.

Patients on or off treatment are at risk of a recurrent VTE and are assumed to experience a maximum of two recurrent VTE events within the model. The risk of a recurrent VTE differs depending upon which treatment the patient is receiving, if any, and whether they are receiving acute treatment or secondary prevention for their initial VTE. All patients who experience a recurrent VTE event are treated acutely with LMWH for 5 days and warfarin for 6 months, regardless of the initial treatment received; no patients receive secondary prevention for a recurrent VTE.

Refer to Section 5 in the ERG report for more information on the model structure developed by the manufacturer and ERG comments on the model.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are

not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Committee noted that the company had presented 2 base-case analyses: 1 for acute treatment and 1 for treatment and prevention of recurrent venous thromboembolism (VTE) ('secondary prevention'). The Committee considered it was appropriate for the company to present base cases for acute treatment and treatment with secondary prevention separately, but that it should be assumed in the secondary prevention base case that treatment would be life-long for most people who require treatment beyond 6 months.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee heard that it was difficult to give a precise estimate of the cost of warfarin monitoring, because the structure of warfarin monitoring services varies widely and there is no definitive average monitoring cost available for the National Health Service (NHS). The Committee concluded that the company's estimate of warfarin monitoring costs was higher than figures previously accepted as reasonable in previous appraisals, but that the Evidence Review Group's (ERG's) was lower.

Warfarin treatment, particularly if life-long, could be expected to reduce quality of life but the extent to which it did so was uncertain. The Committee concluded that although the company's estimate of utility decrement was based on limited evidence, it was the best estimate available and had been accepted as reasonable in previous appraisals.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

None identified.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

Not applicable

What Are the Key Drivers of Cost-effectiveness?

The acute treatment base case incremental cost-effectiveness ratio (ICER) for dabigatran etexilate compared with warfarin was sensitive to the warfarin monitoring costs assumed by the ERG.

In the ERG's exploratory base case for treating and preventing recurrent VTE and the main factors increasing the ICER for dabigatran etexilate compared with warfarin were: assuming life-long secondary prevention resulting in an ICER of £15,634 per quality-adjusted life year (QALY) gained; assuming that warfarin monitoring in the secondary prevention period was less frequent (once every 3 months rather than monthly), resulting in an ICER of £15,208 per QALY gained; and assuming a lower cost of each warfarin monitoring visit resulting in an ICER of £17,419 per QALY gained.

For both acute treatment and secondary prevention of VTE, the Committee noted that neither the company nor the ERG had found any difference in efficacy between the dabigatran etexilate and rivaroxaban treatments in their indirect comparisons, and that the costs were also very similar. This resulted in the ICER estimates being sensitive to small changes in the costs or QALYs.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

The most plausible ICER for dabigatran etexilate compared with warfarin for acute treatment was uncertain, but both the company's and the ERG's exploratory ICER remained in the range which could be considered a cost-effective use of NHS resources; that is, both were under £20,000 per QALY gained. Neither the company nor the ERG had found any significant difference in efficacy between dabigatran etexilate and rivaroxaban for acute treatment of VTE in their indirect comparisons, and the costs were also very similar between these two treatments.

For combined treatment and secondary prevention of VTE, the Committee considered that although the company's base case ICER for dabigatran etexilate compared with warfarin was likely to be too low (£9973 per QALY gained), the ERG's exploratory base case for dabigatran etexilate compared with warfarin (£35,786 per QALY gained) may have overestimated the ICER. The Committee was prepared to accept that the ICER probably lay somewhere between the 2 estimates. The Committee also noted that dabigatran etexilate and rivaroxaban had not been shown to have different efficacy, and their costs were very similar.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the company that manufactures dabigatran etexilate and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from four randomised controlled trials. For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

People welcome having the choice of new oral anticoagulants such as rivaroxaban and dabigatran etexilate, because they avoid the need for the monitoring and dose adjustments associated with warfarin.

Potential Harms

The most common adverse reaction to dabigatran etexilate is bleeding, although indigestion is also common.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, the National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has deep vein thrombosis or pulmonary embolism and the doctor responsible for their care thinks that dabigatran etexilate is the right treatment, it should be available for use, in line with NICE's recommendations.
- NICE has developed tools to help put this guidance into practice (listed below).
    - A costing statement explaining the resource impact of this guidance.

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Dec. 49 p. (Technology appraisal guidance; no. 327).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Dec

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Appraisal Committee Members: Dr Jane Adam (*Chair*), Department of Diagnostic Radiology, St George's Hospital, London; Professor Iain Squire (*Vice-Chair*), Consultant Physician, University Hospitals of Leicester; Dr Graham Ash, Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust; Dr Gerardine Bryant, GP, Swadlincote, Derbyshire; Matthew Campbell-Hil, Lay member; Dr Peter Heywood, Consultant Neurologist, Frenchay Hospital, Bristol; Dr Sharon Saint Lamont, Head of Clinical Quality, NHS England (North); Mr Cliff Snelling, Lay member; Dr Ian Lewin, Honorary Consultant Physician and Endocrinologist, North Devon District Hospital; Dr Louise Longworth, Reader in Health Economics, HERG, Brunel University; Dr Alec Miners, Senior Lecturer in Health Economics, London School of Hygiene and Tropical Medicine; Pamela Rees, Lay member; Dr Ann Richardson, Lay member; Dr Paul Robinson, Medical Director, Merck Sharp & Dohme; Ellen Rule, Director of Transformation and Service Redesign, Gloucestershire CCG; Stephen Sharp, Senior Statistician, University of Cambridge MRC Epidemiology Unit; Dr Peter Sims, GP, Devon; Dr John Watkins, Clinical Senior Lecturer, Cardiff University, Consultant in Public Health Medicine, National Public Health Service Wales; Professor Olivia Wu, Professor of Health Technology Assessment, University of Glasgow

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site.

Availability of Companion Documents

The following are available:

- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Dec. 8 p. (Technology appraisal guidance; no. 327). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site.
- Edwards S, Wakefield V, Thurgar E, Karner C, Marceniuk G. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism: a single technology appraisal. Evidence review group report. London (UK): BMJ Technology Assessment Group (BMJ-TAG); 2014 Aug 18. 312 p. Electronic copies: Available from the NICE Web site.

Patient Resources

The following is available:

- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Dec. 2 p. (Technology appraisal guidance; no. 327). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download as a Kindle or EPUB ebook from the NICE Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide

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